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Investigation of the Reaction Impurities Associated with Methylamphetamine Synthesized Using the Nagai Method

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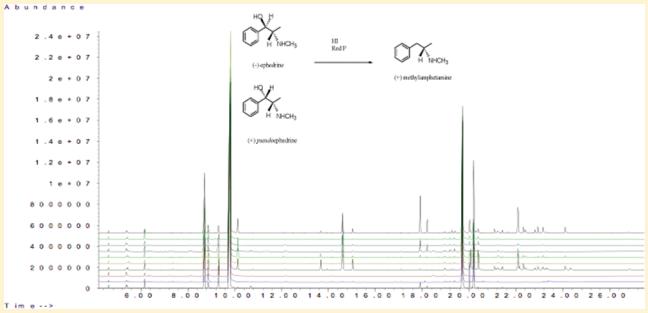
ABSTRACT: The synthesis of methylamphetamine hydrochloride from *l*-ephedrine or *d*-pseudoephedrine hydrochloride via reduction with hydriodic acid and red phosphorus was investigated. Eighteen batches of methylamphetamine hydrochloride were synthesized in six replicate batches using three different reaction times. This allowed the investigation of the variation of impurities in the final product with reaction time. The results obtained have resolved previously conflicting impurity profile data reported in the literature for this synthesis route. The impurity profile was shown to change with reaction time, and all previously reported impurity components were identified but not in all batches. Additionally, 20 batches of methylamphetamine hydrochloride were synthesized from either from *l*-ephedrine or *d*-pseudoephedrine hydrochloride in reactions which were allowed to proceed for 24 h. The impurities present in the resulting batches were investigated, and route-specific impurities present in all batches were identified. Batch-to-batch fluctuations in the resultant chromatographic impurity profile, despite careful synthetic monitoring and control, were also noted.



Methylamphetamine can be synthesized by several routes using either of two precursors, phenyl-2-propanone (P-2-P) or ephedrine/pseudoephedrine hydrochloride. The reduction of ephedrine or pseudoephedrine hydrochloride using hydriodic acid and red phosphorus, known as the Nagai route, is preferred in the Asian and South Asian region. The method is straightforward and can be used for large-scale production (Figure 1).

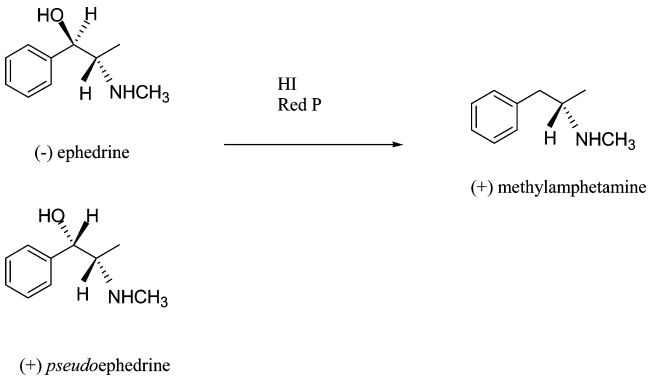


Figure 1. Nagai reaction.

When investigating the existing literature surrounding the Nagai synthesis of methylamphetamine, some confusion was evident in relation to the exact nature of the route-specific impurity products for this synthetic method, as identified using gas chromatography/mass spectrometry (GC/MS).[1−3] This appeared to be due to differences in the reaction time used. Windahl et al.[1] suggested the length of time over which the Nagai reaction proceeded (1/2, 2, or 4 h) had an effect on the level of aziridines and naphthalenes present in the final product. As the reaction time increased, the concentration of aziridines decreased and that of the naphthalenes increased. Tanaka et al.,[2] however, reported the presence of a methylamphetamine dimer formed from the condensation of methylamphetamine and an aziridine.

Table 1. Summary of Samples Produced

reflux time (h)	precursor	no. of repetitive syntheses
0.5	ephedrine	3
0.5	pseudoephedrine	3
2	ephedrine	3
2	pseudoephedrine	3
4	ephedrine	3
4	pseudoephedrine	3
24	ephedrine	10
24	pseudoephedrine	10

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Table 2. Impurities Found in the pH 10.5 Extract of the Sample Synthesized over a 1/2 h Reaction Time

no.	RT	compd[a]	peak *m/z* (base peak in bold)
1	6.187	benzaldehyde	**106**, 105, 77, 51
2	**8.895**	***cis*-1,2-dimethyl-3-phenylaziridine**	**146**, 105, 132, 91
3	**10.422**	***trans*-1,2-dimethyl-3-phenylaziridine**	**146**, 105, 132, 91
4	12.357	ephedrine	**58**, 77, 44, 105, 146
5	13.821	*N*-formylamphetamine	**118**, 72, 44, 91
6	14.688	*N*-formylmethylamphetamine	**86**, 58, 118
7	15.107	*N*-acetylmethylamphetamine	**58**, 100
8	16.592	*N*-formylephedrine	**86**, 87, 58, 77, 100
9	16.895	*N*-acetylephedrine	**58**, 77, 100
10	**20.764**	**methylamphetamine dimer**	**238**, 91, 120, 148, 58
11	**21.025**	**methylamphetamine dimer**	**238**, 91, 120, 148, 58

[a]Impurities previously presented in the literature are in bold.

Table 3. Impurities Found in the pH 6 Extract of the Sample Synthesized over a 1/2 h Reaction Time

no.	RT	compd[a]	peak *m/z* (base peak in bold)
1	6.187	benzaldehyde	**106**, 105, 77, 51
2	**8.830**	***cis*-1,2-dimethyl-3-phenylaziridine**	**146**, 105, 132, 91
3	**10.022**	***trans*-1,2-dimethyl-3-phenylaziridine**	**146**, 105, 132, 91
4	13.682	*N*-formylamphetamine	**118**, 72, 44, 91
5	14.582	*N*-formylmethylamphetamine	**86**, 58, 118
6	15.031	*N*-acetylmethylamphetamine	**58**, 100
7	16.422	*N*-formylephedrine	**86**, 87, 58, 77, 100
8	16.757	*N*-acetylephedrine	**58**, 77, 100

[a]Impurities previously presented in the literature are in bold.

Table 4. Impurities Found in the pH 10.5 Extract of the Sample Synthesized over a 2 h Reaction Time

no.	RT	compd[a]	peak *m/z* (base peak in bold)
1	6.144	benzaldehyde	**106**, 105, 77, 51
2	12.439	ephedrine	**58**, 77, 44, 105, 146
3	13.924	*N*-formylamphetamine	**118**, 72, 44, 91
4	14.572	*N*-formylmethylamphetamine	**86**, 58, 118
5	15.001	*N*-acetylmethylamphetamine	**58**, 100
6	**20.051**	**1,3-dimethyl-2-phenylnaphthalene**	**232**, 217, 202, 77
7	**20.198**	**1-benzyl-3-methylnaphthalene**	**232**, 217, 202, 58
8	**20.365**	***N*-methyl-*N*-(α-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
9	**20.491**	***N*-methyl-*N*-(α-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
10	**21.003**	**methylamphetamine dimer**	**238**, 91, 120, 148, 58
11	**22.425**	**(*Z*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77
12	**23.425**	**(*E*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77

[a]Impurities previously presented in the literature are in bold.

The presence of the methylamphetamine dimer was not reported by Windahl. The work of Ko et al.,[3] which involved a 5 h reaction

Table 5. Impurities Found in the pH 6 Extract of the Sample Synthesized over a 2 h Reaction Time

no.	RT	compd[a]	peak *m/z* (base peak in bold)
1	6.154	benzaldehyde	**106**, 105, 77, 51
2	**8.810**	***cis*-1,2-dimethyl-3-phenylaziridine**	**146**, 105, 132, 91
3	**10.002**	***trans*-1,2-dimethyl-3-phenylaziridine**	**146**, 105, 132, 91
4	13.672	*N*-formylamphetamine	**118**, 72, 44, 91
5	14.593	*N*-formylmethylamphetamine	**86**, 58, 118
6	15.021	*N*-acetylmethylamphetamine	**58**, 100
7	**19.999**	**1,3-dimethyl-2-phenylnaphthalene**	**232**, 217, 202, 77
8	**20.176**	**1-benzyl-3-methylnaphthalene**	**232**, 217, 202, 58
9	**20.312**	***N*-methyl-*N*-(α-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
10	**20.471**	***N*-methyl-*N*-(α-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
11	**22.425**	**(*Z*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77
12	**23.425**	**(*E*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77

[a]Impurities previously presented in the literature are in bold.

Table 6. Impurities Found in the pH 10.5 Extract of the Sample Synthesized over a 4 h Reaction Time

no.	RT	compd[a]	peak *m/z* (base peak in bold)
1	6.16	benzaldehyde	**106**, 105, 77, 51
2	13.640	*N*-formylamphetamine	**118**, 72, 44, 91
3	14.571	*N*-formylmethylamphetamine	**86**, 58, 118
4	14.999	*N*-acetylmethylamphetamine	**58**, 100
5	**20.008**	**1,3-dimethyl-2-phenylnaphthalene**	**232**, 217, 202, 77
6	**20.249**	**1-benzyl-3-methylnaphthalene**	**232**, 217, 202, 58
7	**20.301**	***N*-methyl-*N*-(α-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
8	**20.426**	***N*-methyl-*N*-(α-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
9	**22.425**	**(*Z*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77
10	**23.425**	**(*E*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77

[a]Impurities previously presented in the literature are in bold.

time, corroborated the presence of naphthalenes, as well as propanone and propenamide (reported by Windahl et al.[1]), and the absence of the aziridines and the methylamphetamine dimer.

The preparative methods employed as part of this program were taken from published materials which are accessible to, and used by, the clandestine chemist.[4] In order to complete this study the diastereoisomers pair, (*l*) ephedrine and (*d*) pseudoephedrine were used as starting reagents which yield only (*d*) methylamphetamine, the more potent isomer. Two impurity extracts (pH 6.0 and pH 10.5) of the synthesized methylamphetamine hydrochloride were obtained using an extraction method developed in our laboratories.[5] The acidic and basic extracts for each production batch were then analyzed using a previously published GC/MS method.[5] The combination of both acidic and basic impurity profiles covers a broad spectrum of basic *and* acidic impurities present in each synthetic batch.

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The impurities previously reported in the literature have been explored during the first phase of this study by varying the reaction time between 1/2, 2, and 4 h. Eighteen batches of methylamphetamine hydrochloride were synthesized by the Nagai method with six batches from each of the three reaction times. During the second phase of the study the extent of variation in chromatographic impurity profiles obtained across 20 repetitively synthesized batches of material prepared using the Nagai method was investigated. For these samples, the reaction conditions were precisely replicated and the synthesis was allowed to proceed for a total of 24 h to ensure complete conversion to the required product.

Table 7. Impurities Found in the pH 6 Extract of the Sample Synthesized over a 4 h Reaction Time

no.	RT	compd[a]	peak *m/z* (base peak in bold)
1	6.142	benzaldehyde	**106**, 105, 77, 51
2	**8.798**	***cis*-1,2-dimethyl-3-phenylaziridine**	**146**, 105, 132, 91
3	**10.002**	***trans*-1,2-dimethyl-3-phenylaziridine**	**146**, 105, 132, 91
5	14.591	*N*-formylmethylamphetamine	**86**, 58, 118
6	15.030	*N*-acetylmethylamphetamine	**58**, 100
7	**20.018**	**1,3-dimethyl-2-phenylnaphthalene**	**232**, 217, 202, 77
8	**20.186**	**1-benzyl-3-methylnaphthalene**	**232**, 217, 202, 58
9	**20.301**	***N*-methyl-*N*-(α-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
10	**20.416**	***N*-methyl-*N*-(α-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
11	**22.45**	**(*Z*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77
12	**23.425**	**(*E*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77

[a]Impurities previously presented in the literature are in bold.

EXPERIMENTAL SECTION

Reagents and Materials. Reagents and materials were purchased from commercial suppliers. Toluene and ethyl acetate was purchased from Fisher Scientific. Hydrochloric acid (37%), glacial acetic acid, and sulfuric acid (95−97%) were purchased from Riedel de Haën (Germany). Sodium chloride, sodium carbonate, sodium hydroxide pellets (≥97.5%), and magnesium sulfate were purchased from GPR (Poole, England). Eicosane, *l*-ephedrine hydrochloride, *d*-pseudoephedrine hydrochloride, red phosphorus, and hydriodic acid (50%) were purchased from Sigma-Aldrich. Distilled water was obtained from an in-house water purification system. Potassium phosphate monobasic (KH_2PO_4), sodium phosphate dibasic dihydrate ($Na_2HPO_4{\cdot}2H_2O$,) and sodium acetate (CH_3CO_2Na) were purchased from Fluka.

Synthesis. A 100 mL round-bottom flask was filled with either ephedrine hydrochloride or pseudoephedrine hydrochloride (6.05 g, 30 mmol, 1 equiv). Also added to the flask were red phosphorus (1.61 g, 52 mmol, 1.74 equiv) and 50% hydriodic acid (14 mL, 180 mmol, 6 equiv). Once fully charged, a condenser was attached to the flask, and the mixture was refluxed for either 1/2, 2, 4, or 24 h to produce the desired samples as listed in Table 1. Once the reflux was completed the flask was allowed to cool and the contents diluted with an equal volume of water. Any remaining red phosphorus was removed by filtration.

A 25% NaOH solution (24 mL, 100.8 mmol) was slowly added, and the crude methylamphetamine base was extracted with toluene (3 × 20 mL). The combined organic layers were dried over magnesium sulfate and the volatiles removed in vacuo to reveal the methylamphetamine base as a clear to pale yellow colored oil. The product was very clean with no distillation necessary. Analysis was in agreement with our previously published data for IR, ^{1}H NMR, and ^{13}C NMR.[5]

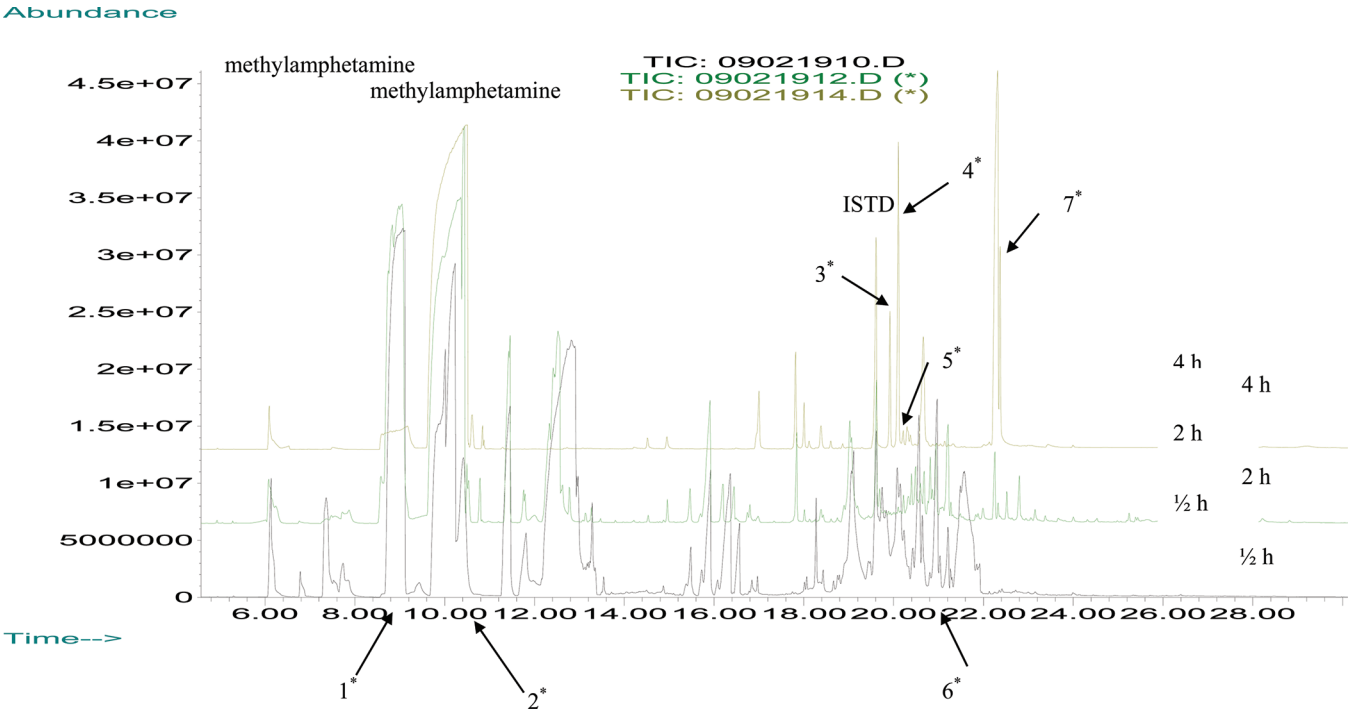

Figure 2. Overlay of the impurity profiles at pH 10.5 for the three reaction times: 1*, *cis*-1,2-dimethyl-3-phenylaziridine; 2*, *trans*-1,2-dimethyl-3-phenylaziridine; 3*, 1,3-dimethyl-2-phenylnaphthalene; 4*, 1-benzyl-3-methylnaphthalene; 5*, *N*-methyl-*N*-(α-methylphenethyl)amino-1-phenyl-2-propanone; 6*, methylamphetamine dimer; 7*, (*Z*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide and (*E*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide.

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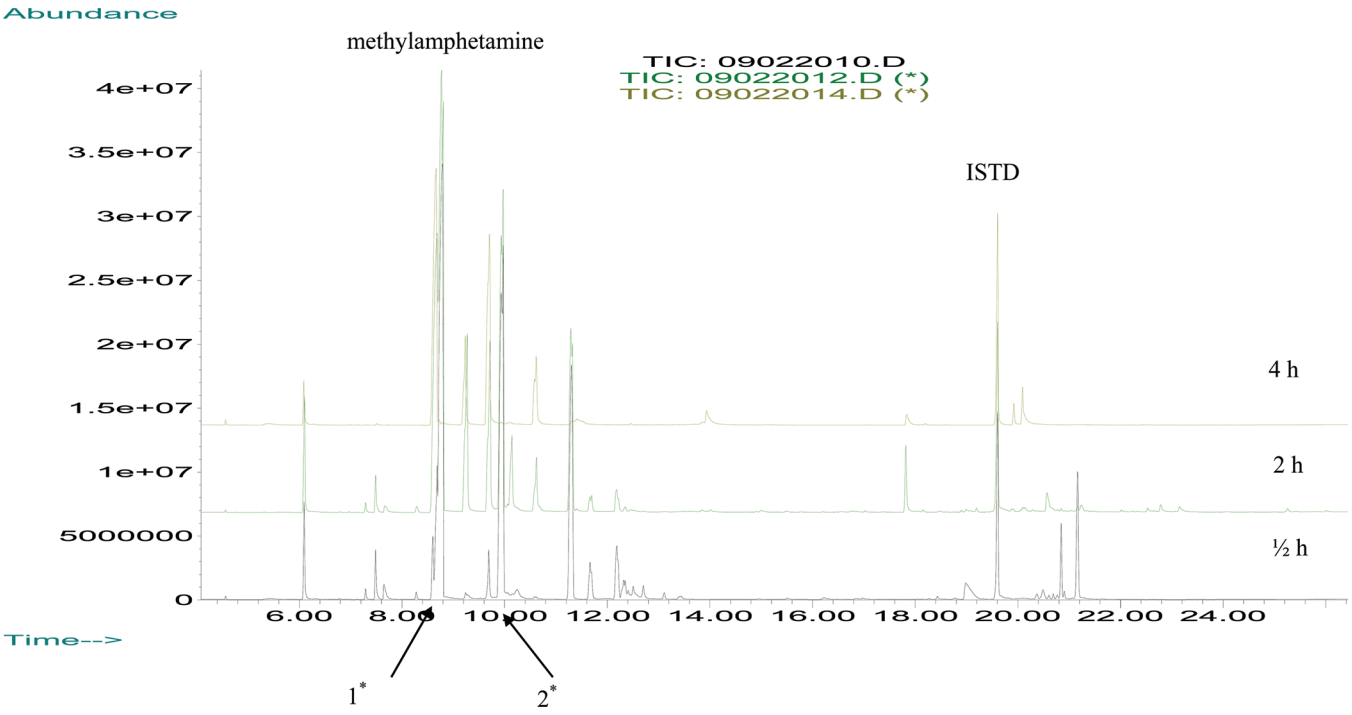

Figure 3. Overlay of the impurity profiles at pH 6 for the three reaction times: 1*, *cis*-1,2-dimethyl-3-phenylaziridine; 2*, *trans*-1,2-dimethyl-3-phenylaziridine.

Table 8. Impurities Found by Windahl et al. (Ref 1), Tanaka et al. (Ref 2), and This Study in the Synthesis of Methylamphetamine by the Nagai Route

impurities	Windahl[a]	Tanaka[b]	this work
cis-1,2-dimethyl-3-phenylaziridine	√		√ (1/2, 2, 4 h)
trans-1,2-dimethyl-3-phenylaziridine	√		√ (1/2, 2, 4 h)
methylamphetamine dimer		√	√ (1/2, 2 h)
1,3-dimethyl-2-phenylnaphthalene	√		√ (2, 4, 24 h)
1-benzyl-3-methylnaphthalene	√		√ (2, 4, 24 h)
isomers of *N*-methyl-*N*-(α-methylphenylethyl)amino-1-phenyl-2-propanone	√		√ (2, 4, 24 h)
isomers of *N*-methyl-*N*-(α-methylphenethyl)-3-phenyl propenamide	√		√ (2, 4, 24 h)

[a]Ref 1. [b]Ref 2.

Table 9. Impurities from the Basic Extract (Phosphate Buffer pH 6.0) of the Sample Synthesized over a 24 h Reaction Time

no.	RT	compd	peak *m*/*z*
1	8.716	1-phenyl-2-propanone	**43**, 91, 134
2	8.894	amphetamine	**44**, 91, 134
3	9.323	1-phenyl-1,2-propanedione	**105**, 77, 51, 43
4	10.138	3-phenyl-3-buten-2-one	**103**, **146**, **91**
5	10.211	*N*,*N*-dimethylbenzylamine	**58**, 135, 107, 79
6	13.673	*N*-formylamphetamine	**118**, 72, 44, 91
7	14.603	*N*-formylmethylamphetamine	**86**, 58, 97, 118
8	15.053	*N*-acetylmethylamphetamine	**58**, 100
9	**20.041**	**1,3-dimethyl-2-phenylnaphthalene**	**232**, 217, 202, 58
10	**20.208**	**1-benzyl-3-methylnaphthalene**	**232**, 217, 202, 58
11	**20.355**	***N*-methyl-*N*-(α-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
12	20.407	*N*-benzoylmethylamphetamine	**105**, 162, 77, 91

IR ν_{max} (film)/cm^{-1}: 1605 (N−C), 1454, 1373, 1155, 741, 697. ^{1}H NMR (400 MHz, $CDCl_3$): δH 1.08 (d, 3H, J = 8.0 Hz, CH_3), 2.42 (s, 3H, CH_3), 2.62 (dd, 1H, J = 20.0, 8.0 Hz, CH), 2.65 (dd, 1H, J = 20.0, 4.0 Hz, CH), 2.71−2.83 (m, 1H, CH), 7.17−7.37 ppm (m, 5H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 34.0, 43.5, 56.4, 126.2, 128.4, 129.3, 139.5 ppm.

Conversion of the methylamphetamine base to the hydrochloride salt was achieved by dissolving the base in toluene (50 mL) and bubbling through anhydrous hydrogen chloride gas. The resulting white precipitate was filtered, washed with toluene, and dried under high vacuum to produce methylamphetamine hydrochloride as a white salt. The typical yield obtained was 55−82%. Analysis was in agreement with our previously published data for IR, ^{1}H NMR, and ^{13}C NMR.[5]

IR ν_{max} (KBr)/cm^{-1}: 3419 (N−H), 2971, 2731, 2461 (C−C), 1603 (N−C). ^{1}H NMR (400 MHz, D_2O): δH 1.22 (d, 3H, J = 8.0 Hz, CH_3), 2.64 (s, 3H, CH_3), 2.87 (dd, 1H, J = 24.0, 8.0 Hz, CH), 3.03 (dd, 1H, J = 20.0, 8.0 Hz, CH), 3.44−3.50 (m, 1H, CH), 7.25−7.38 (m, 5H, C_6H_5). ^{13}C NMR (100 MHz, D_2O): δ 14.8, 29.9, 38.8, 56.4, 127.5, 129.1, 129.5, 135.8 ppm.

Extraction of Impurities from Methylamphetamine Hydrochloride. *Basic Extract.* A solution of 0.1 M phosphate buffer (pH 7.0) was brought to pH 10.5 by the addition of 10% Na_2CO_3. Synthesized methylamphetamine hydrochloride (100 mg) was homogenized with a mortar and pestle and dissolved in the pH 10.5 phosphate buffer (2 mL). The mixture was sonicated (5 min) within a sonication bath and vortexed (2 min). Ethyl acetate (0.4 mL) containing eicosane (as an internal standard at 0.05 mg/mL concentration) was added. After centrifugation (5 min), the organic layer was transferred into a microvial insert for GC/MS analysis.

Acidic Extract. A solution of 0.1 M acetate buffer (pH 8.16) was brought to pH 6.0 by addition of acetic acid. The acidic impurities from the synthesized methylamphetamine were extracted

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Table 10. Impurities from the Acidic Extract (Acetate Buffer pH 10.5) of the Sample Synthesized over a 24 h Reaction Time

no.	RT	compd	peak *m/z*
1	7.252	acetic acid	**43**, 60, 91, 134
2	9.521	amphetamine	**44**, 91, 65, 134
3	10.912	*N*-(1-methyl-2-phenylethylidene) methenamine	**56**, 91, 65, 39, 77
4	11.131	dimethylamphetamine (DMA)	**72**, 91, 56, 42
5	11.738	(*Z*) (1-phenylpropan-2-one oxime)	**91**, 149, 116, 131
6	11.780	(*E*) (1-phenylpropan-2-one oxime)	**91**, 131, 116, 149
7	12.47	3,4-dimethyl-5-phenyloxazolidine	**71**, 56, 91
8	12.51	3,4-dimethyl-5-phenyloxazolidine	**71**, 56, 91
9	13.662	*N*-formylamphetamine	**118**, 72, 44, 91
10	14.321	bibenzyl	**91**, 182
11	14.593	*N*-formylmethylamphetamine	**86**, 58, 118
12	15.032	*N*-acetylmethylamphetamine	**58**, 100
13	18.127	benzylmethamphetmine	**91**, 148, 65, 105
14	17.911	*cis*-3,4-diphenyl-3-buten-2-one	**179**, 178, 222, 221
15	18.21	*trans*-3,4-diphenyl-3-buten-2-one	**179**, 178, 222, 221
16	18.440	*N*-*β*-(phenylisopropyl)benzyl methyl ketimine	**91**, 160, 119, 65, 77, 207
17	**20.051**	**1,3-dimethyl-2-phenylnaphthalene**	**232**, 217, 202, 77
18	20.117	*N*-benzoylamphetamine	**105**, 77, 148, 91, 118
19	**20.208**	**1-benzyl-3-methylnaphthalene**	**232**, 217, 202, 58
20	**20.344**	***N*-methyl-*N*-(*α*-methylphenethyl) amino-1-phenyl-2-propanone**	**238**, 91, 105, 190, 120
21	20.417	*N*-benzoylmethylamphetamine	**105**, 162, 77, 91
22	22.361	*N*,*N*-di-(*β*-phenylisopropyl) formamide	**190**, 91, 58, 119, 77, 105
23	**22.425**	**(*Z*)-*N*-methyl-*N*-(*α*-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77
24	**23.425**	**(*E*)-*N*-methyl-*N*-(*α*-methylphenethyl)-3-phenylpropenamide**	**131**, 91, 58, 103, 188, 77

using this buffer in an identical fashion to that described above for the basic extraction.

GC/MS Analysis. GC/MS analysis was performed using an Agilent 6890 GC and a 5973 mass selective detector (MSD). The mass spectrometer was operated in the electron ionization mode at 70 eV. Separation was achieved with a nonpolar capillary column (DB-1MS, 25 m × 0.2 mm i.d., 0.33 μm, J&W Scientific) with helium as the carrier gas at a constant flow rate of 1.0 mL/min. The oven temperature program (adapted from Inoue et al.[6]) started at 50 °C for 1 min, was increased to 300 °C at a rate of 10 °C/min, and then held at 300 °C for 15 min. A 1 μL aliquot of the impurity extract was injected in the splitless mode with a purge time of 1 min. The injector and the GC interface temperatures were maintained at 250 and 300 °C, respectively. Mass spectra were obtained in full scan mode (30−550 amu).

Peak Identification. The identity of compounds within the total ion chromatograms was confirmed based on matches identified using the NIST spectral library and through reference to the published literature. The main peak at 10 min is methylamphetamine, and the peak at 19.7 min is the internal standard, eicosane, in each chromatogram presented.

RESULTS AND DISCUSSION

Phase One: Synthesis Using 1/2, 2, or 4 h Reaction Times. Six batches from each of the three reaction times were prepared, and the acidic and basic impurities within the samples were extracted and analyzed.

1/2 h Reaction. Tables 2 and 3 provide details of the impurities from the phosphate and acetate buffer extracts, respectively, of methylamphetamine synthesized over a 1/2 h reaction time. Highlighted are the presence of the aziridines as suggested by Windahl et al.[1] and methylamphetamine dimers as suggested by Tanaka et al.,[2] the latter being extracted only using the phosphate buffer.

2 h Reaction. Tables 4 and 5 detail the impurities from the phosphate and acetate buffer extracts, respectively, of methylamphetamine synthesized over a 2 h reaction time. The presence

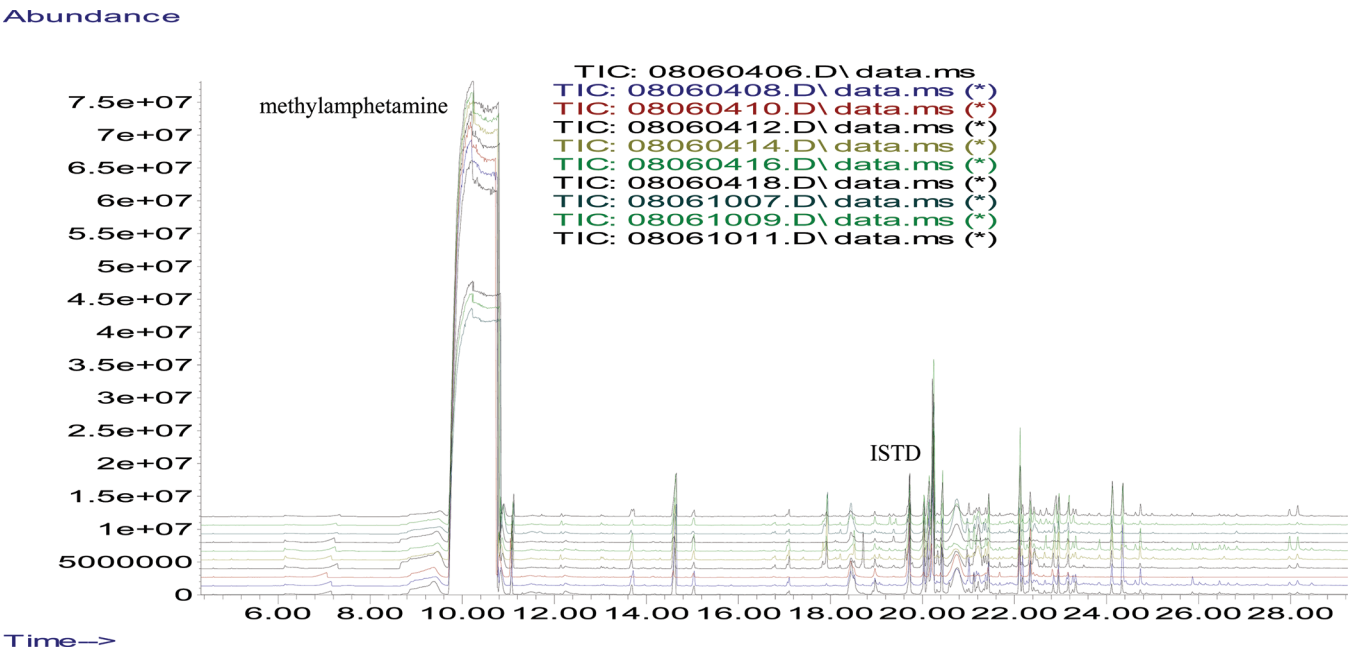

Figure 4. Overlay of the impurity profiles from the 10 samples synthesized over 24 h from ephedrine extracted at pH 10.5.

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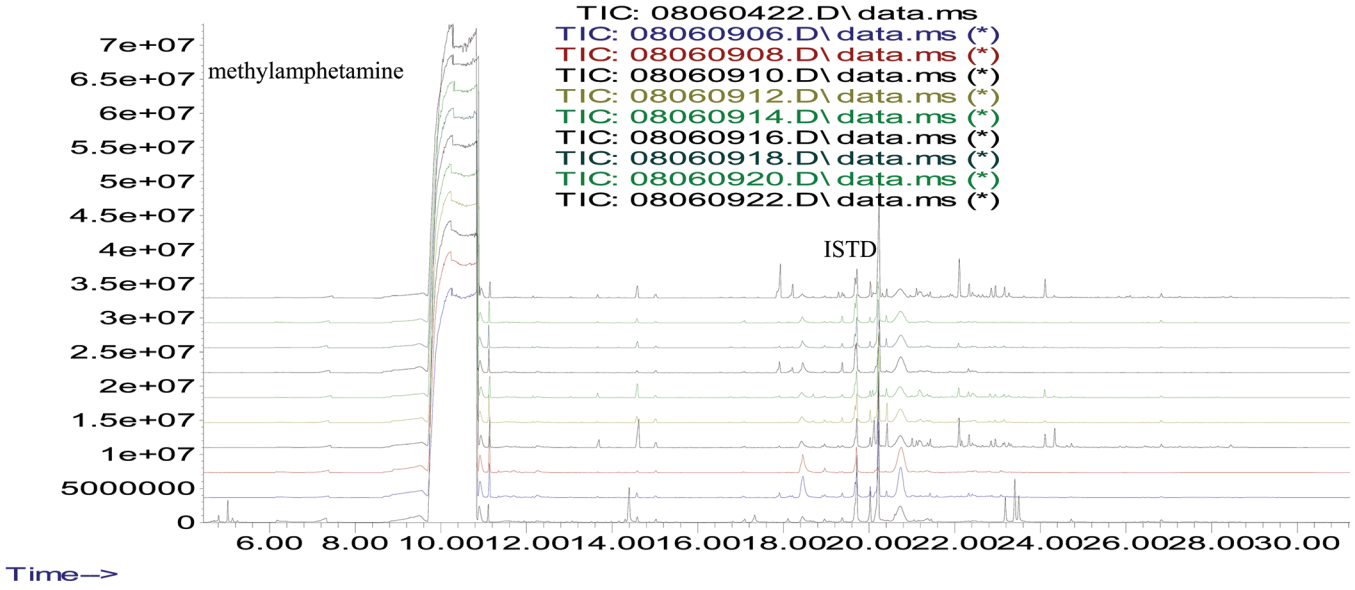

Figure 5. Overlay of the impurity profiles from the 10 samples synthesized over 24 h from pseudoephedrine extracted at pH 10.5.

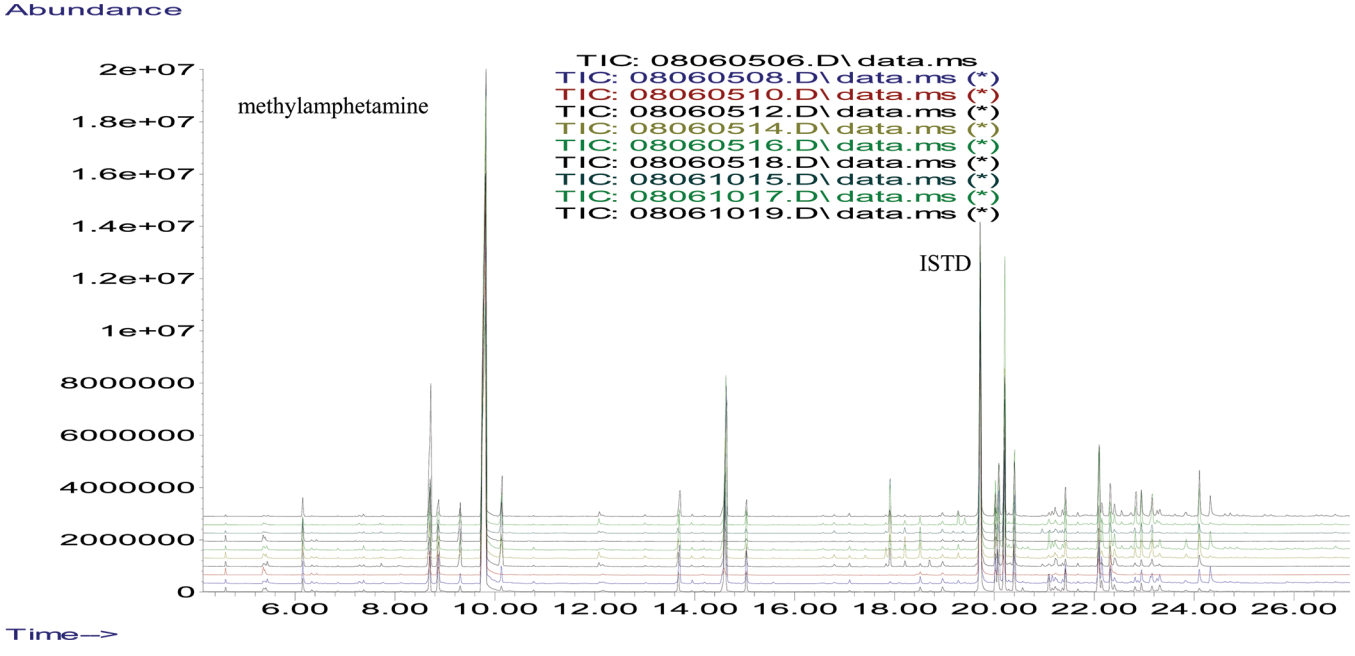

Figure 6. Overlay of the impurity profiles from the 10 samples synthesized over 24 h from ephedrine extracted at pH 6.0.

of the naphthalene compounds was observed in both extracts. The methylamphetamine dimer was only in evidence in the basic extracts, and the aziridines were only present in the acidic extracts. Also noted was the formation of the propanone and propenamide species, as suggested by Windahl et al.[1]

4 h Reaction. Tables 6 and 7 present the impurities from the phosphate and acetate buffer extracts, respectively, of methylamphetamine synthesized using a 4 h reaction time. Both naphthalene compounds are present in both extracts, whereas the aziridines are only evident in the acetate buffer. The methylamphetamine dimer is now absent from the profile in both extracts.

Figures 2 and 3 present the impurity profiles at each pH of methylamphetamine synthesized using the three different reaction times (1/2, 2, and 4 h) for the Nagai route. The change in impurity profiles over time for both pH extracts is clearly apparent from each illustration.

Windahl et al.[1] suggested that, as the reaction time increased, the quantity of the aziridines decreased and the quantity of the two naphthalenes increased. This study confirmed these results. Although Windahl et al.[1] did not report the presence of the methylamphetamine dimer in any reaction batches, this study did find this compound present in both the 1/2 and 2 h reaction batches, but not the 4 or 24 h reaction runs, thus confirming that the methylamphetamine dimer was formed but cannot be considered as a route-specific impurity. These observations corroborate the claim of Tanaka et al.[2] that the methylamphetamine dimer is formed from the

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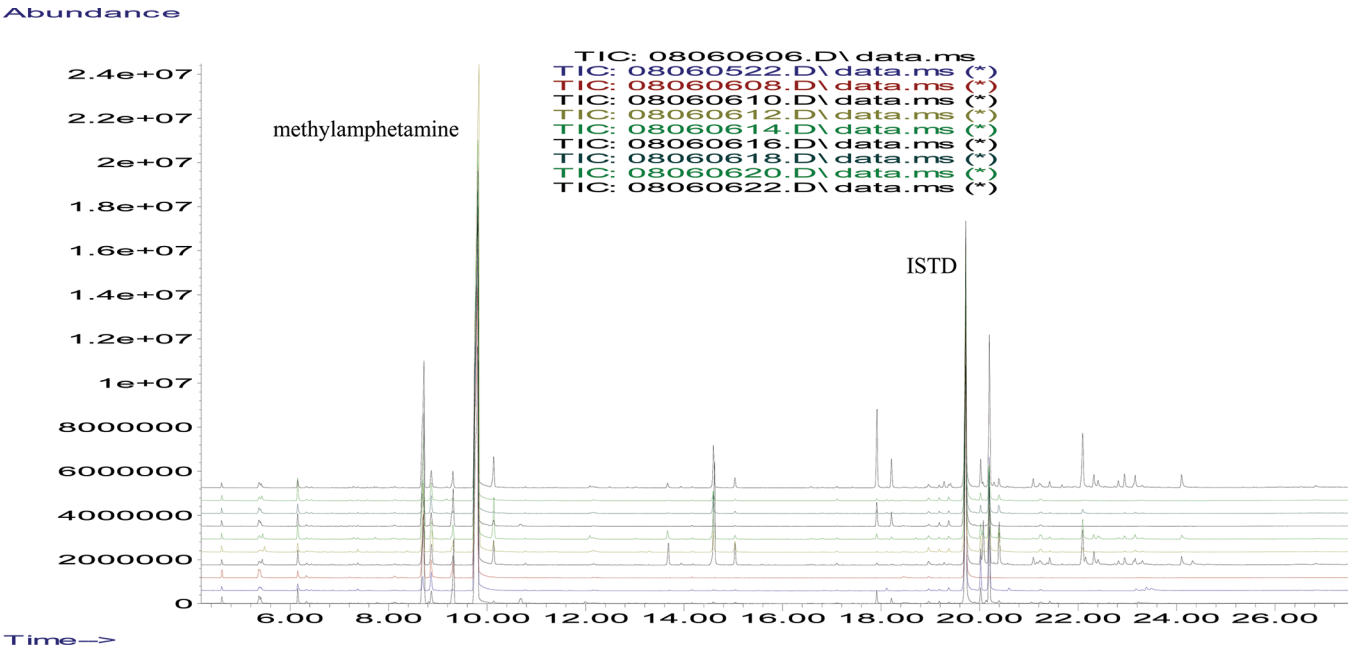

Figure 7. Overlay of the impurity profiles from the 10 samples synthesized over 24 h from pseudoephedrine extracted at pH 6.0.

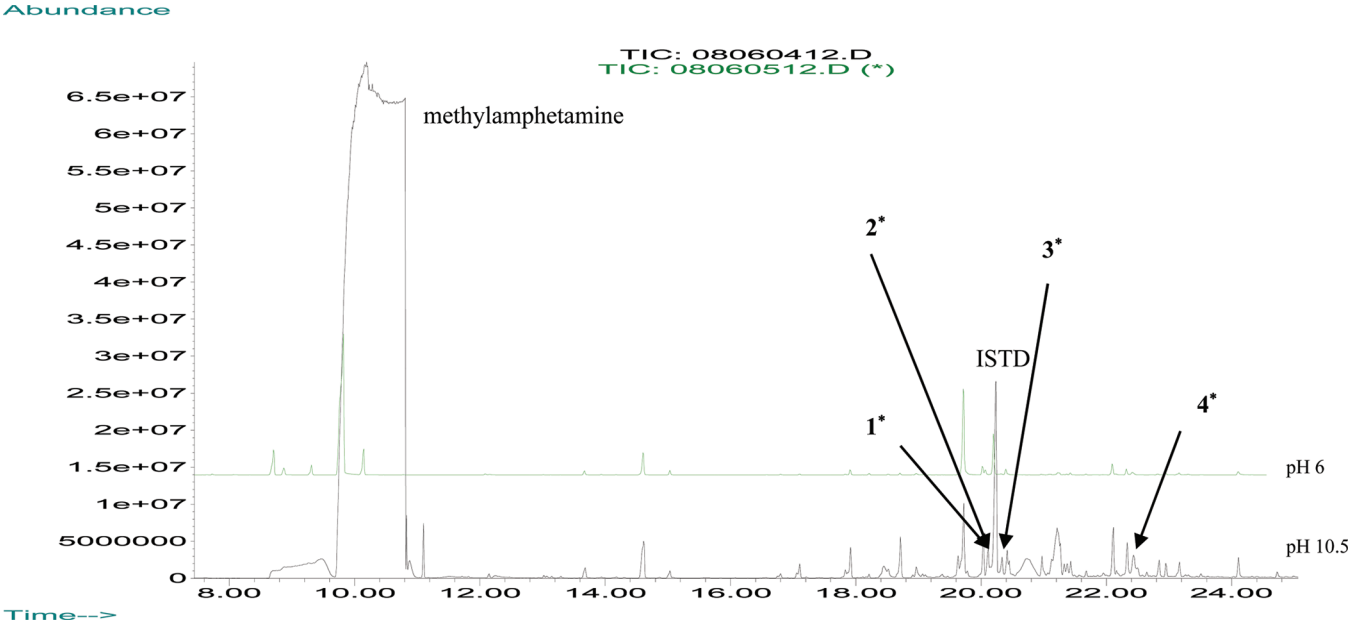

Figure 8. Overlay of the impurity profiles for both extracts of methylamphetamine synthesized over 24 h reaction time: 1*, 1,3-dimethyl-2-phenylnaphthalene; 2*, 1-benzyl-3-methylnaphthalene; 3*, *N*-methyl-*N*-(α-methylphenethyl)amino-1-phenyl-2-propanone; 4*, (*Z*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide and (*E*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide.

condensation of methylamphetamine and aziridine: as the reaction time increases, the quantity of aziridine decreases and the methylamphetamine dimer cannot be formed as readily. It should be noted that Tanaka et al.[2] did not perform any time study reactions for the Nagai route. A summary of the impurities found in this and previous studies is presented in Table 8. Accordingly, it is pleasing to note that this study has clarified the previous literature in relation to impurities presented for the Nagai route.

Phase Two: Synthesis Using a 24 h Reaction Time. Ephedrine hydrochloride and pseudoephedrine hydrochloride were each used to prepare 10 samples, respectively, of methylamphetamine hydrochloride using the Nagai method, as previously described. In each case, the reflux reaction was carried out for 24 h. Each sample was extracted using both the acidic and basic buffers and analyzed by GC/MS. The extracted impurities are listed in Tables 9 and 10 for each extract.

The chromatographic results for each of the 20 batches synthesized via the Nagai method are presented in Figures 4−7. Visual comparison of the impurity profiles demonstrates some obvious variation between the 20 batches, particularly within the 18−21 min range in the pH 10.5 extraction. In particular, the peak heights of some compounds relative to each other were noticed to vary from sample to sample indicative of the varying concentrations of these compounds, despite the reaction

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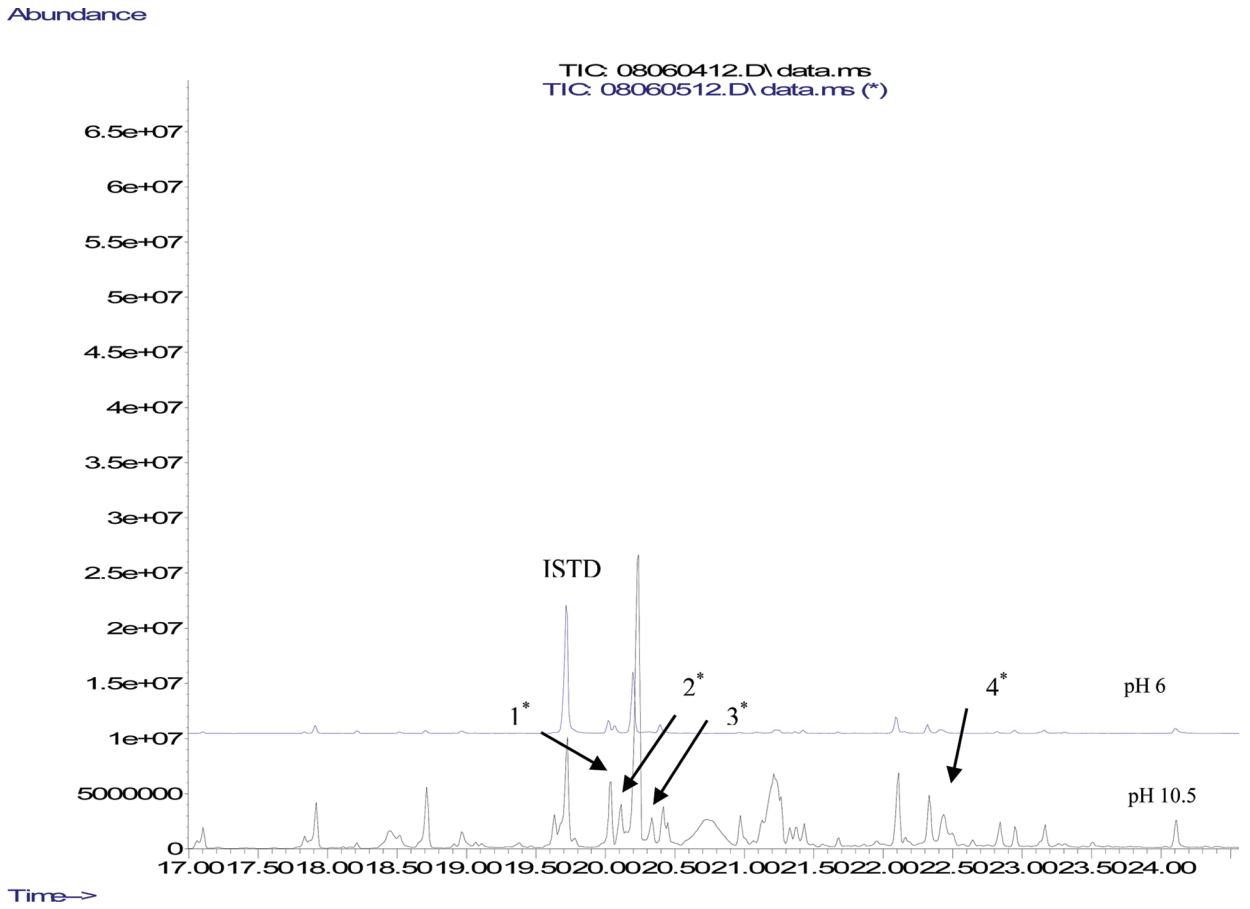

Figure 9. Overlay of the impurity profiles for both extracts of methylamphetamine synthesized over 24 h highlighting the area between 17 and 24 min: 1*, 1,3-dimethyl-2-phenylnaphthalene; 2*, 1-benzyl-3-methylnaphthalene; 3*, *N*-methyl-*N*-(α-methylphenethyl)amino-1-phenyl-2-propanone, 4* (*Z*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide and (*E*)-*N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide.

conditions being carefully controlled and the use of the same batch of laboratory grade starting material. Of note is that the batches synthesized using pseudoephedrine hydrochloride as the precursor produced cleaner chromatograms for both acidic and basic extracts.

Six impurities were detected in all of the methylamphetamine samples synthesized by the Nagai method over 24 h regardless of starting product and are revealed in Figures 8 and 9, which present both extracts of one synthetic batch. These impurities are 1,3-dimethyl-2-phenylnaphthalene, 1-benzyl-3-methylnaphthalene, two isomers of *N*-methyl-*N*-(α-methylphenethyl)amino-1-phenyl-2-propanone, and two isomers of *N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide.

CONCLUSIONS

The timed synthetic study undertaken for the Nagai route has explained and clarified the differing results obtained in the previously published literature. The methylamphetamine dimer is formed from the condensation of methylamphetamine and aziridine: as the reaction time increases, the quantity of aziridine decreases, and therefore, the dimer cannot be formed as readily.

Six specific impurities (1,3-dimethyl-2-phenylnaphthalene and 1-benzyl-3-methylnaphthalene, the isomers of *N*-methyl-*N*-(α-methylphenethyl)amino-1-phenyl-2-propanone, and the isomers of *N*-methyl-*N*-(α-methylphenethyl)-3-phenylpropenamide) were detected in methylamphetamine synthesized by the Nagai method but only occurred in samples where a reaction time of 2 h or greater is employed. These included the previously reported naphthalenes. Although the aziridines (*cis*-1,2-dimethyl-3-phenylaziridine and *trans*-1,2-dimethyl-3-phenylaziridine) and the methylamphetamine dimer have been reported as route-specific markers by previous researchers they may or may not always be present, depending on the time allowed for the reaction to proceed.

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Notes

The authors declare no competing financial interest.

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